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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,782	02/06/2002	Gary L. Griffiths	329549	5555

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/066,782	GRIFFITHS ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,48 and 49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,11,12,14 and 48* is/are rejected.

7)☒ Claim(s) *5-6, 8-10, 13 and 49* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 4/17/2007 in response to the previous Non-Final Office Action (2/26/2007) is acknowledged and has been entered.

Claims 1-14 and 48-49 are currently pending and under consideration.

Rejections Withdrawn:

The rejection of claims 1-14 and 48-49 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01 is withdrawn in view of Applicants amendments.

The rejection of claims 1, 4-5 and 11 on the ground of nonstatutory obviousness double patenting as being unpatentable over claims 1, 4-5, 16-18 and 24-25 of US Patent 6,962,702 is withdrawn in view of Applicants filing of a terminal disclaimer.

New Rejections upon further Consideration:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear whether a cell line which produces an antibody having the exact chemical identity of MIN-14 or 734 is known or publicly available, or can be reproducibly isolated without

undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one or ordinary skill in the art could not be assured of the ability to practice the claimed invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3rd ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See, 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of this application, access to the invention will be afforded to one determined by the Commissioner to be entitled thereto;
(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of the patent;
(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;
(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an addition means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundack, 773 F.2d. 1216, 227 USPQ 90 (CAFC) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 11 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al. (WO 91/08770, 1991, of record) in view of Barbet et al. (US 5,256,395, 1993).

Hansen teaches a method for increasing the target-specific toxicity of a drug, comprising pretargeting an enzyme to a human target cell; and administering a cytotoxic drug or a prodrug form thereof known to act at the target site, wherein the enzyme is capable of forming the active therapeutic agent (page 4, line 13 to page 5, line 2 and page 46, lines 4-5). Specifically, the WO document teaches that the enzyme is pretargeted to a target cell using an antibody-enzyme conjugate

(page 5, lines 14-15). With regards to the enzyme, the WO document teaches that suitable enzymes include, but are not limited to, glucuronidase, beta-glucosidase, beta-lactamase, cellulose, dextranase, fructose, aminopeptidase and lysozyme (page 9, lines 22-31). With regards to the antibody, the WO document teaches that the antibodies include, but are not limited to, monoclonal antibodies, antibodies having dual or multiple antigen or epitope specifities or fragments thereof including hybrid fragments (page 6, lines 22-30 and page 7, lines 11-22). Moreover, the WO document teaches that bispecific antibodies can also be used as the antibody-enzyme conjugate, wherein the bispecific antibody contains at least one binding site specific to an antigen at the target site and at least one other binding site specific to the enzyme component of the antibody-enzyme conjugate, thereby obviating the need to covalently conjugate the enzyme to the antibody (page 8, lines 24-37). Regarding the drug, the WO document teaches that the one type of anti-tumor drug that can be converted to a substrate for glucurodinase is an anthracycline glycoside referred to as epirubicin (page 14, lines 25-35). In addition, Handen teaches that the clearance of the antibody-enzyme conjugate and/or the substrate-enzyme conjugate can be accelerate by using a second antibody complex which recognizes the conjugate and enhances the rate of uptake by macrophages (page 25, lines 20-33). Thus, while Hansen does not explicitly teach that the epirubicin is detoxified to form an intermediate of lower toxicity, whereby the detoxified intermediate is reconverted to its more toxic form by the pretargeted enzyme, the claimed limitation does not appear to result in a manipulative difference in the method steps when compared to the prior art disclosure because the specification teaches (page 9, 3rd full paragraph) that drugs such as epirubicin which are detoxified in the liver to glucuronides such as epirubicin are suitable candidates for the site specific enhancement methods of the present invention. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). In the instant case, the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Hansen does not explicity teach that the bispecific antibody comprises an arm which targets a low molecular weight hapten that is conjugate to said enzyme or administering a low molecular weight hapten that is conjugated to said enzyme.

Barbet et al. teach immunogical reagents consisting of a) antibody or fragment conjugates having both anti-cell specificity and anti-hapten specificity; and b) a synthetic tracer containing at least two hapten attached to radioactive isotopes, paramagnetic ions, drugs or toxins, wherein the reagents are capable of binding to target cells in a specific way, and the tracer localizes preferentially on the membrane of antigen-bearing cells even in the presence of excess antibody conjugate (column 4, lines 22-47).

Thus, it would have been prima facie obvious at the time the invention was made to modify the bispecific antibody as taught by Hansen et al. to include a bispecific antibody as taught by Barbet et al., and further to modify the pretargeting method as taught by Hansen et al. to include administration of an hapten-enzyme conjugate in view of the teachings Barbet et al. One would have been motivated to do so because Barbet et al. teach that the hapten conjugates localizes preferentially on the membrane of antigen-bearing cells even in the presence of excess antibody conjugate. Thus, one would have a reasonable expectation of success that by modifying the bispecific antibody as taught by Hansen et al. to include a bispecific antibody as taught by Barbet et al., and further modifying the pretargeting method as taught by Hansen et al. to include administration of an hapten-enzyme conjugate in view of the teachings Barbet et al., one would achieve a method of improving pretargeting an enzyme to the membrane of an antigen-bearing cell..

Claims 12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al. (WO 91/08770, 1991) in view Barbet et al. (US 5,256,395, 1993) and in further view of Griffiths et al (WO 96/40245, 1996, of record).

Hansen in view of Barbet et al. teach, as applied to claims 1-4, 11 and 48 above, a method for increasing the target-specific toxicity of a drug, comprising (a) pretargeting an enzyme to a human target cell, wherein said pretargeting comprises (1) administering a bispecific antibody or fragment thereof, wherein one arm of the bispecific antibody is targeted against a target site antigen and a second arm is targeted against a low molecular weight hapten that is conjugated to said enzyme and (2) administering a low molecular weight hapten that is conjugated to said enzyme; (b)

administering a second antibody complex which recognizes the conjugate and enhances the rate of clearance and (3) administering a cytotoxic drug or a prodrug form thereof known to act at the target site, wherein the enzyme is capable of forming the active therapeutic agent

Hansen in view of Barbet et al. does not explicitly teach that the antibody used during the clearing step is an anti-idiotypic antibody, wherein the anti-idiotypic antibody is specific for the paratope of the monoclonal antibody conjugate to the enzyme.

Griffiths et al. teach an improvement in *in vivo* pretargeting methods, wherein the improvement involves the administration of a clearing agent that binds to the primary binding site of the primary targeting species, whereby substantially only non-localized primary targeting species are cleared and targeted primary targeting species are not removed from the target site (page 6, lines 7-35). For example, the WO document teaches that when the primary targeting species is an antibody, the clearing agent comprises an antibody which recognizes the antigen binding region (paratope) of the targeting antibody, i.e., the clearing agent comprises an anti-idiotypic second antibody (page 9, lines 1-12 and page 10, line 38 to page 11, line 6).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method taught by Hansen in view of Barbet et al. with an anti-idiotypic antibody in view of Griffiths et al teachings of an improved method of in vivo pretargeting. One would have been motivated to do so because of Griffiths et al. teach that anti-idiotypic antibodies allow for the selective removal of non-localized targeting species and not the removal of targeting species from the target site. Thus, one of ordinary skill in the art would have a reasonable expectation that by using an anti-idiotypic antibody in the clearance step taught by Hansen in view of Barbet, one would achieve a method of improving pretargeting an enzyme-antibody conjugate for therapeutic purposes.

Conclusion

Claims 5-6, 8-10, 13 and 49 appear to be free of the prior art, but are objected to as being dependent from a rejected independent claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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BF